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General Information

Key Personnel (in addition to PI): **First Name:** Konstantinos
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Degree: MD, PhD
Primary Affiliation: Beth Israel Deaconess Medical Center

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00207766 - ACCENT II - A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long Term Treatment of Patients With Fistulizing CROHN'S Disease
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Defining a therapeutic drug window in patients treated with infliximab for fistulizing Crohn's disease.

Narrative Summary:
Two pivotal randomized-controlled trials clearly showed superior healing rates of fistulas after induction and maintenance infliximab treatment compared to placebo in patients with fistulizing Crohn's disease (CD). Serum infliximab trough concentrations have been related to favorable objective therapeutic outcomes, such as endoscopic healing. Nevertheless, there are limited data on the therapeutic window and role of therapeutic drug monitoring in fistula healing. The aim of the study is to investigate the association between serum infliximab trough concentration and positive therapeutic outcomes in patients with fistulizing CD.

Scientific Abstract:
Background: Infliximab is effective treatment for fistulizing Crohn's disease (CD). Recent exposure-response relationship studies have revealed a positive correlation between high serum infliximab concentration and favorable therapeutic outcomes, although there are only limited data regarding fistulizing CD.
Objective: To define the therapeutic window for adequate serum infliximab concentration associated with favorable therapeutic outcomes in patients with fistulizing CD for either induction or maintenance therapy.
Study Design: Post-hoc analysis of the ACCENT II study.
Participants: Patients with CD who were assessed for a fistula response following infliximab induction (n=282) or maintenance therapy (n=139).
Main outcome measure(s): Association between infliximab concentration at week 2, 6 and 14 with fistula response or complete fistula response at week 14 and association between infliximab trough concentration at week 14, 22, 30, 38, 46 and 54 with fistula response or complete fistula response at week 54.
Statistical Analysis: Descriptive statistics will be provided with medians and interquartile range for continuous variables and frequency and percentage for categorical variables. A receiver operating characteristic analysis will be performed for infliximab concentrations to trace thresholds associated with outcomes of interest. Infliximab concentrations will be compared between groups with the Mann-Whitney U and Kruskal Wallis test, as appropriate. Univariate and multivariate analyses will be performed to identify variables associated with outcomes of interest.

Brief Project Background and Statement of Project Significance:
Fistulas can develop in up to 50% of patients with Crohn's disease (CD), with perianal fistulas being the most common. (1) The cornerstone of pharmacological treatment for fistulizing CD is anti-tumor necrosis factor (TNF) therapy, specifically infliximab. (2) Two pivotal randomized-controlled trials clearly showed superior healing rates after induction and maintenance infliximab treatment compared to placebo. (3,4) Recent studies have revealed an exposure-response relationship suggesting a positive correlation between high serum anti-TNF drug concentration and favorable therapeutic outcomes including clinical, biomarker, and endoscopic remission. (5-10) Nevertheless, there are limited data on the therapeutic window and role of therapeutic drug monitoring (TDM) in fistula healing. (11) Moreover, as pharmacological treatment options in patients with fistulizing CD remain limited, emphasis has to be given to rational decision-making and optimization of therapies utilizing a TDM-based therapeutic approach. This project, by defining the adequate infliximab concentration for better therapeutic outcomes in patients with fistulizing CD would be crucial in better understanding necessary drug concentrations. It could serve as an important first step towards the implementation of proactive TDM in daily clinical practice and towards a 'treat-to-trough' therapeutic approach. This could potentially improve care and reduce the substantial social and economic burden to the community by preventing future CD-related hospitalizations and surgeries.

Specific Aims of the Project:
Specific Aim 1:
To investigate the association between serum infliximab concentration at week 2, 6 and 14 with fistula response, defined as a reduction of at least 50 percent from base line in the number of draining fistulas and complete fistula response, defined as the absence of draining fistulas, at week 14.

Specific Aim 2:
To investigate the association between serum infliximab trough concentration at week 14, 22, 30, 38, 46 and 54 with fistula response and complete fistula response at week 54.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Post-hoc analysis of the ACCENT II (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen in Patients with Fistulizing Crohn's Disease) study, a multicenter, double-blind, randomized, placebo-controlled trial, regarding only the patients who received infliximab (active drug) during induction (n=282) or maintenance therapy (n=139). (4)

Main Outcome Measure and how it will be categorized/defined for your study:
• Main outcome measures of interest include:
1. Fistula response, defined as a reduction of at least 50% from base line in the number of draining fistulas at week 14 and 54.
2. Complete fistula response, defined as the absence of draining fistulas, at week 14 and 54.
• Secondary outcome measures of interest include:
1. C-reactive protein (CRP) normalization at week 14 and 54 in patients with an elevated CRP (>5 mg/L) at week 0.
2. Clinical remission, defined as a CD Activity Index (CDAI) score of ?150, at week 14 and 54.
3. Clinical response, defined as a reduction from a baseline CDAI of 220 or higher by at least 25% and 70 points, at week 14 and 54.
4. Duration of rectovaginal fistula closure.
5. Composite remission, defined as both CRP normalization and complete fistula response, at week 14 and 54.
6. Loss of response throughout week 54.
7. Fistula response to treatment with increased infliximab dose at week 54.
8. Acute and/or delayed hypersensitivity infusion reactions throughout week 54.
9. Infections requiring antimicrobial treatment throughout week 54.
10. Primary non-response defined as lack of fistula response at either week 10 or week 14.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Main predictor/independent variables associated with outcomes of interest include:
• Serum infliximab concentration at week 2, 6 and 14 associated with main and secondary outcomes of interest.
• Serum infliximab trough concentration at week 14, 22, 30, 38, 46 and 54 associated with outcomes of interest.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Other variables associated with outcomes of interest include:
• Gender
• Age
• Disease duration
• Previous segmental resection
• CDAI at week 0
• CRP at week 0
• Concomitant immunomodulators (thiopurines / methotrexate)
• Type (single or multiple) and location (perianal, abdominal and rectovaginal) of fistulas
• Smoking history
• Antibodies to infliximab (ATI) at week 14, 30 and 54.

Statistical Analysis Plan:
Descriptive statistics will be provided with medians and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables. A receiver operating characteristic (ROC) analysis will be performed for infliximab concentrations to trace thresholds associated with outcomes of interest. Optimal thresholds will be chosen by using the Youden index, which maximizes the sum of the specificity (SP) and sensitivity (SN) of the ROC curve as previously described.8 SN, SP, positive predictive value, and negative predictive value will be also calculated. Infliximab concentrations at week 2, 6, 14, 22, 30, 38, 46 and 54 will be compared between groups with the Mann-Whitney U test. Serum infliximab concentrations will be categorized also into quartiles. Rates of fistula response and complete fistula response as well as other (secondary) outcome measures of interest at week 14 and 54 will be compared across infliximab serum concentration quartiles with the chi-square test (linear-by-linear association). The Kruskal-Wallis and the chi-square test will be used to compare continuous or discrete variables, respectively, across quartile groups. The Mann-Whitney U test and the chi-square test or the Fisher exact test will be used for univariate analysis to identify quantitative or categorical variables associated with

outcomes of interest, respectively. For endpoints defined by time to an event, such as loss of response, life table methods will be employed and the log-rank test will be used for comparisons between treatment groups. To determine the independent effects of variables associated with outcomes of interest, a multiple binary logistic regression will be then performed including variables with a P value <0.05 from univariate analysis, based on the Backward Wald selection method. The results will be expressed as odds ratio (OR) with 95% confidence intervals, followed by the corresponding P value. Results will be considered statistically significant when P <0.05. All statistical analyses will be performed by using the R and SAS statistical software.

Project Timeline:
It is estimated that it will take 3-4 months to review the appropriate data. Statistical analyses will take another 3-4 months, while manuscript preparation will take approximately another 3-4 months. Consequently, the whole project will be completed in 9-12 months.

Dissemination Plan:
Presentation of the results to national and international medical congresses including Digestive Disease Week (DDW), Advances in IBD (AIBD), American College of Gastroenterology (ACG), European Crohn's and Colitis Organization (ECCO) and publication of the data in a high impact medical journal such as the American Journal of Gastroenterology, Clinical Gastroenterology and Hepatology, or the Journal of Crohn's and Colitis.

Bibliography:
1. Gecse KB, Sebastian S, Hertogh G, et al. Results of the Fifth Scientific Workshop of the ECCO [II]: Clinical Aspects of Perianal Fistulising Crohn's Disease-the Unmet Needs. J Crohns Colitis 2016;10(7):758-65.
2. Yassin NA, Askari A, Warusavitarne J, et al. Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. Aliment Pharmacol Ther 2014;40(7):741-9
3. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398-405.
4. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350:876-85.
5. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology 2014;147:1296-1307.
6. Ungar B, Levy I, Yavne Y, et al. Optimizing anti-TNF? therapy: Serum levels of infliximab and adalimumab associate with mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2016;14:550-557.e2.
7. Roblin X, Marotte H, Rinaudo M, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2014;12:80-4.
8. Papamichael K, Van Stappen T, Vande Casteele N, et al. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. Clin Gastroenterol Hepatol 2016;14:543-9.
9. Reinisch W, Colombel JF, Sandborn WJ, et al. Factors associated with short- and long-term outcomes of therapy for Crohn's disease. Clin Gastroenterol Hepatol 2015;13:539-547.
10. Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut 2014;63:1721-7.
11. Davidov Y, Ungar B, Bar-Yoseph H, et al. Association of induction infliximab levels with clinical response in perianal Crohn's disease. J Crohns Colitis. 2016 Oct 4. pii: jjw182. [Epub ahead of print].